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Analysis of Association between Norepinephrine Transporter Gene Polymorphisms and Personality Traits of NEO-FFI in a Japanese Population

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Objective Norepinephrine is an important chemical messenger that is involved in mood and stress in humans, and is reabsorbed by the norepinephrine transporter (NET). According to Cloninger's theory, the noradrenergic system mediates the personality trait of reward dependence. Thus far, although association studies on NET gene polymorphisms and Cloninger's personality traits have been reported, they yielded inconsistent results. Therefore, in the present study we investigated whether or not the 1287G/A, -182T/C and -3081A/T polymorphisms of the NET gene (*SLC6A2*) are associated with reward dependence-related traits, as assessed by the five-factor model.

Methods After written informed consent was obtained from participants, the three NET gene polymorphisms were analyzed by polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP), and personality was assessed by the Neuroticism Extraversion Openness-Five Factor Inventory (NEO-FFI) in 270 Japanese university students.

Results A significant relation was found between the -3081A/T functional promoter polymorphism and NEO-FFI scores: those with the T allele exhibited a lower extraversion (E) score than those without the T allele (Mann-Whitney U-test: $z=-3.861$, $p<0.001$). However, there was no correlation between the other NET gene polymorphisms and E score, and no association with other dimensions and these three polymorphisms.

Conclusion We conclude that the -3081A/T functional polymorphism in the NET gene may affect the extraversion of reward dependence-related traits, as measured by NEO-FFI. However, we used only the shortened version of NEO-PI-R in this study. Further investigations are necessary using the full version of self-rating personality questionnaires. **Psychiatry Investig 2015;12(3):381-387**

Key Words Norepinephrine transporter, Gene polymorphism, NEO-FFI, Personality.

INTRODUCTION

Norepinephrine is one of the catecholamines, and is important as a neurotransmitter in the sympathetic peripheral nervous system.[1] Noradrenergic pathways support arousal, mood, attention and reaction to stress.[2] The action of norepinephrine is controlled by norepinephrine binding proteins such as the norepinephrine transporter (NET) and adrenergic receptors,[3] where norepinephrine reuptake is mainly performed by NET. NET is a monoamine transporter, i.e., a Na^+/Cl^- dependent neurotransmitter transporter,[4] and it is a major target for the treatment of mood, anxiety and depression disorders.[5] It has been shown that the NET knockout mice exhibit resistance to stress-induced depressive-like changes in behavior and brain neurotrophin expression.[6] Furthermore, a recent psychophysiological study using positron emission tomography (PET) scan demonstrated that NET is involved in loss aversion, and individuals with lower thalamic NET showed stronger aversion to financial loss.[7] These findings indicate the possibility that NET is related to human personality traits.

The human NET gene (*SLC6A2*) is located on chromosome 16q12.2,[8] spanning approximately 45 kb and consisting of 14

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exons.[9] A previous study has shown that some personality formation genes are implicated in susceptibility to various abnormal types of human behavior, including depression and attention deficit.[10] Therefore, among the several known NET gene polymorphisms, we focused on the 1287G/A (rs5569), -182T/C (rs2242446) and -3081A/T (rs28386840) polymorphisms, for which an association with psychiatric disorders such as depression and attention deficit hyperactivity disorder (ADHD) has been indicated.[11-15] Stober et al.[16] detected a highly polymorphic silent 1287G/A polymorphism in the NET gene, which was located in exon 9. The -182T/C polymorphism is located in the 5' flanking promoter region,[17] and this region of the NET gene contains several cis-elements of importance for transcriptional activity.[18] The T allele of the -3081A/T polymorphism, comprising a single nucleotide change of A to T at -3081 upstream of the transcription initiation site of the human NET gene, significantly decreased the NET promoter function compared to the A allele, as reported by Kim et al.[13]

Thus far, association studies of the NET gene polymorphism and personality traits have been reported, but they yielded inconsistent results.[19-24] Cloninger proposed that the three heritable dimensions of personality comprise novelty seeking, harm avoidance, and reward dependence,[25] and in subsequent research, the Temperament and Character Inventory (TCI) was developed, which has four temperament dimensions (novelty seeking, harm avoidance, reward dependence, and persistence) and three character dimensions (self-directedness, cooperativeness, and self-transcendence), to assess the personality traits.[26] Originally, according to Cloninger's theory, the three heritable dimensions of novelty seeking, harm avoidance, and reward dependence are related to different neurotransmitter systems, and the noradrenergic system mediates reward dependence of individuals.[25,27] A previous study found a probable association between NET gene polymorphism and reward dependence.[19] However, similar studies into NET gene polymorphisms have failed to find significant associations, and show a possible association with novelty seeking, but not reward dependence.[20-24] In addition, several studies reported that in the five-factor model of personality, reward dependence primarily relates to extraversion.[28,29] Therefore, if NET gene polymorphism contributes to the personality dimension of reward dependence, it might be associated with reward dependence-related traits in the five-factor model. All of these research findings are based on Cloninger's model. Hence, it is suggested that it is necessary to examine the relevance of NET gene polymorphism and the personality dimension of reward dependence using widely varying self-report personality questionnaires, thereby enabling more detailed analysis.

The Neuroticism Extraversion Openness-Five Factor Inventory (NEO-FFI) is one of the self-report questionnaires based on the five-factor model of personality that are used to examine the relationship between genes and personality. NEO-FFI is used to assess the five major dimensions of personality traits by means of a questionnaire comprising 60 items, it being a shortened version of the Revised NEO Personality Inventory (NEO-PI-R). The five dimensions are Neuroticism (N), Extraversion (E), Openness (O), Agreeableness (A) and Conscientiousness (C).[30] This questionnaire is superior in comprehensiveness, and enables assessment of the five personality dimensions needed for an efficient psychological profile of the individual.[31]

Therefore, in the present study, we investigated whether or not the 1287G/A, -182T/C and -3081A/T polymorphisms of the NET gene are associated with reward dependence-related traits, as assessed by NEO-FFI.

METHODS

Subjects

The participants comprised 270 volunteers. In order to rule out confounding factors such as age and general intelligence level differences, all candidates for this research consisted of students in Azabu University, Japan. The mean age was 19.61±0.93 (mean±SD) years (male: 19.67±0.94 years; female: 19.56±0.92 years).[32] The subject's epidemiologic data is shown in Table 1. The study was approved by the ethics committee of Azabu University, Japan. After obtaining written informed consent, blood samples were obtained from all the subjects. In addition, we performed the Japanese version of the NEO-FFI for all subjects. The validity and reliability of the Japanese version of the NEO-FFI have already been confirmed among the Japanese population.[33]

DNA analysis

We performed extraction and purification of genomic DNA by the phenol/chloroform method. Three NET gene polymorphisms were genotyped by means of polymerase chain reac-

Table 1. Subject's epidemiologic data

Sex, male/female	117/153
Age	19.61±0.93 (19–25)
NEO-FFI scores	
Neuroticism	30.18±7.90 (6–47)
Extraversion	25.16±7.14 (5–44)
Openness	28.87±5.59 (13–46)
Agreeableness	28.95±6.23 (5–44)
Conscientiousness	26.29±5.67 (4–44)

The figures on the table are showed as the mean±SD (range). NEO-FFI: Neuroticism Extraversion Openness-Five Factor Inventory

tion (PCR)-restriction fragment length polymorphism (RFLP) according to the methods of Inoue et al.[12,34] and Suzuki et al.[22] Genomic DNA was amplified with the following primers: 1287 G/A (forward: 5'-TTCAGGGAGACCCTAATTCC-3', reverse: 5'-TTGACTTTATTGAAATGCGGC-3'), -182T/C (forward: 5'-CCATTTGGGGCAGGCGAAAGT-3', reverse: 5'-CGCTGACGGGACGCAGGGTTCCCAGCCAAG-3'), -3081A/T (forward: 5'-CCTGGGGCTCTGCTGTTAGC-3', reverse: 5'-CCTGGAAGCAATCGTTGGGG-3'). The PCR cycling conditions were: 10 min of denaturation at 95°C, followed by 35 cycles of denaturation for 30s at 95°C, annealing for 30s at 53°C (1287G/A), 57°C (-182T/C), or 60°C (-3081A/T), and extension for 30s at 72°C, followed by 7 min of extension at 72°C. The PCR products (241 bp for 1287G/A, 176 bp for -182T/C, and 295 bp for -3081A/T) were digested with a restrictive enzyme, *Sau96* I, *Sty* I (New England Biolabs, Tokyo, Japan), or *BsrS* I (Promega Corp, Madison, USA), and the digested products were subjected to electrophoresis on 12.5% polyacrylamide gels and visualized using the ethidium bromide staining method. Genotypes were determined according to fragment sizes: 1287G/A: G/G=113 bp+76 bp+31 bp+21 bp, G/A=113 bp+97 bp+76 bp+31 bp+21 bp, A/A=113 bp+97 bp+31 bp; -182T/C: T/T=176 bp, T/C=176 bp+146 bp+30 bp, C/C=146 bp+30 bp, and -3081A/T: A/A=198 bp+97 bp, A/T=295 bp+198 bp+97 bp, T/T=295 bp (Figure 1).

Statistical analyses

The Hardy-Weinberg disequilibrium was assessed using a chi-square test. We compared the NEO-FFI scores among the NET genotypes by performing statistical analysis using Mann-Whitney *U*-test. Because there were few subjects with the homozygotes for the minor allele, the subjects were divided into two groups regarding each polymorphism for statistical analyses, i.e., G/G versus G/A+A/A for 1287G/A and T/T versus T/C+C/C for -182T/C. In the -3081A/T polymorphism, as it was reported that the T allele causes decreased NET promoter function,[13] we compared T-carriers with A/A homozygotes (A/ A versus A/T+T/T). A p-value was set at 0.05 (two-tailed). With five comparisons (Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness), a p-value<0.01 (0.05/5) was considered significant using the Bonferroni correction. Statistical analyses were performed using SPSS 12.0J for Windows.

RESULTS

The genotype frequencies of the NET gene polymorphisms were as follows: 1287G/A (G/G: 164, G/A: 89, A/A: 17); -182T/C (T/T: 110, T/C: 128, C/C: 32) and -3081A/T (A/A: 76, A/T: 129, T/T: 65). The NET genotype distribution was in Hardy-Weinberg equilibrium (1287G/A: χ^2 (1)=1.071, p=0.301; -182T/C: χ^2 (1)=0.321, p=0.571; and -3081A/T: χ^2 (1)=0.496, p=0.481). No gender difference among NET genotypes were detected (1287G/A: χ^2 (2)=1.591, p=0.451; -182T/C: χ^2 (2)=0.168, p=0.919; and -3081A/T: χ^2 (2)=0.393, p=0.821).

The NEO-FFI scores in university students grouped by NET gene polymorphisms are shown in Table 2 and Figure 2. There was no significant effect of the 1287G/A on the five dimension

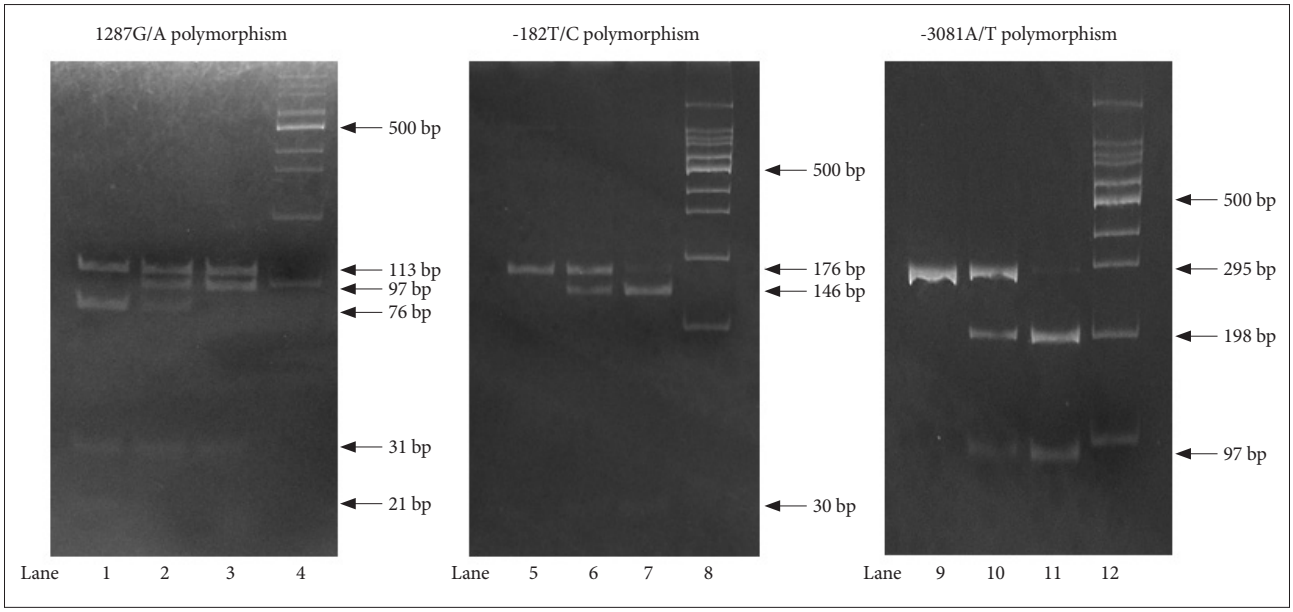

Figure 1. Representative results for the norepinephrine transporter gene polymorphisms with the PCR-RFLP method. Lane 1 is a G/G type. Lane 2 is a G/A type. Lane 3 is a A/A type. Lane 5 is a T/T type. Lane 6 is a T/C type. Lane 7 is a C/C type. Lane 9 is a T/T type. Lane 10 is a A/T type. Lane 11 is a A/A type. Lane 4, 8, and 12 are 100 bp DNA Ladder. PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism.

Table 2. NEO-FFI scores in Japanese subjects grouped by the norepinephrine transporter gene polymorphisms

SNP	Genotype	n	N	E	O	A	C
1287G/A	G/G	164	29.55±8.14	25.51±6.62	28.66±5.45	29.22±5.80	26.32±5.60
	G/A+A/A	106	31.15±7.46	24.62±7.88	29.19±5.82	28.54±6.83	26.24±5.79
-182T/C	T/T	110	29.89±8.36	25.70±6.24	29.19±6.05	29.48±6.33	25.73±6.03
	T/C+C/C	160	30.37±7.59	24.79±7.70	28.64±5.26	28.59±6.15	26.67±5.39
-3081A/T	A/A	76	28.78±8.43	27.74±6.36	29.64±5.99	29.91±5.86	27.14±5.30
	A/T+T/T	194	30.73±7.64	24.15±7.19*	28.56±5.42	28.58±6.34	25.95±5.78

*p<0.001, significantly lower scores compared with A/A genotype (Mann-Whitney U-test). NEO-FFI scores are showed as the mean±SD. NEO-FFI: Neuroticism Extraversion Openness-Five Factor Inventory, SNP: single nucleotide polymorphism, N: neuroticism, E: extraversion, O: openness, A: agreeableness, C: conscientiousness

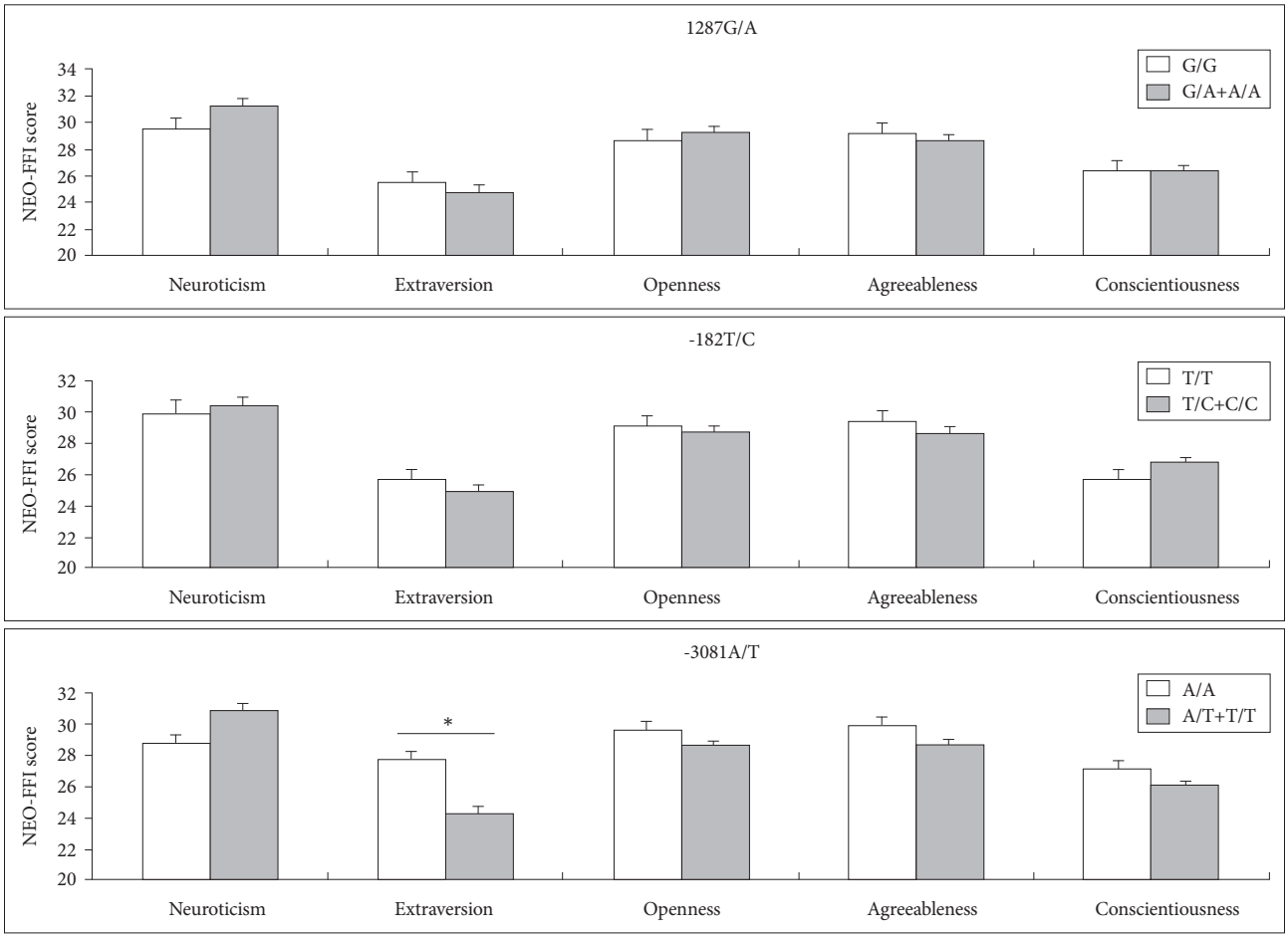

Figure 2. Effects of the norepinephrine transporter gene polymorphisms on the NEO-FFI scores. *p<0.001, the scores of extraversion were significantly different between the subjects with and without T allele (Mann-Whitney U-test). NEO-FFI: Neuroticism Extraversion Openness-Five Factor Inventory.

scores of NEO-FFI (N: p=0.081, E: p=0.622, O: p=0.352, A: p=0.682, and C: p=0.911). Furthermore, there was no significant effect of the -182T/C on the five dimension scores of NEO-FFI (N: p=0.638, E: p=0.258, O: p=0.222, A: p=0.368, and C: p=0.261). On the other hand, there was a significant association with extraversion among genotypes of -3081A/T, and the A/T+T/T genotypes (with T allele) had significantly lower scores than the A/A genotype (without T allele) (z=-3.861, p<0.001). However, no significant associations were observed with the other four dimension scores (N: p=0.061, O: p=0.143, A: p=0.168, and C: p=0.128).

DISCUSSION

It is possible that a norepinephrine transporter (NET) gene polymorphism is involved in the reward dependence-related

personality trait. Although all previous research findings are based on Cloninger's model, it is thought necessary to examine the relationship between NET gene polymorphisms and the personality dimension of reward dependence, as assessed by not only Cloninger's model but also various other personality assessments, such as the five-factor model. In this study, we examined the relationship between three NET gene polymorphisms (1287G/A, -182T/C, and -3081A/T) and NEO-FFI, which is one of the self-report questionnaires based on the five-factor model of personality. The genotype and allele frequencies of the NET gene polymorphisms observed in this study were consistent with the genotype [1287G/A: χ^2 (2)= 0.695, p=0.707; -182T/C: χ^2 (2)=2.274, p=0.321] and allele [1287 G/A: χ^2 (1)=0.061, p=0.805; -182T/C: χ^2 (1)=1.029, p=0.310] frequencies observed in the HapMap (http://hapmap.ncbi.nlm.nih.gov/index.html.ja) Japanese population, respectively. Although the frequencies of the -3081A/T polymorphism observed in the Japanese population have not been reported in the HapMap, data analysed in this study did not differ from other Japanese populations of healthy subjects [genotype: χ^2 (2)=1.994, p=0.369; allele: χ^2 (1)=0.051, p=0.822].[22]

The main result of our study suggests that there is a significant relationship between the -3081A/T polymorphism and extraversion, and that individuals with the A/T and T/T genotype groups exhibited lower scores than ones with the A/A genotype group. It is worth noting that the -3081A/T polymorphism is one of the functional variants. Kim et al.[13] reported that the T allele of this polymorphism significantly decreases the NET promoter function compared with the A allele. Because of this function, the -3081A/T polymorphism affects norepinephrine concentration in synaptic clefts in the brain, and consequently may also affect personality traits. Several studies investigated the relevance of Cloninger's model and the five-factor model as indicators of personality assessment, and indicated that there is a positive correlation between reward dependence in Cloninger's temperament dimensions and extraversion in the five personality dimensions.[28,29] Meanwhile, low reward dependence has been related to high noradrenergic activity.[25] Therefore, lower extraversion in subjects with the A/T and T/T genotypes may be explained by elevated extracellular levels of norepinephrine related to reduced functioning of the NET. Yamamoto and Novotney have described NET reuptake of not only norepinephrine but also dopamine in the medial prefrontal cortex (MPFC), and through this, norepinephrine terminals regulate extracellular dopamine concentrations.[35] Furthermore, several previous studies suggest that because dopamine transporter activity is insufficient for the dopamine nerve terminals in the prefrontal cortex,[36] NET plays a role in dopamine reuptake instead.[37] These findings indicate that the NET function influences dopaminergic activity. Intriguingly, several studies have reported that the extraversion personality trait shows a significant association with genetic polymorphisms in the dopaminergic system, e.g., dopamine D2 and dopamine D4 receptors.[38-41] Therefore, the -3081A/T functional polymorphism of the NET gene also affects the extracellular levels of dopamine, and consequently the dopaminergic system may be reflected in the personality trait of extraversion to which this polymorphism is related.

To our knowledge, research involving analysis of the relation of NET gene polymorphism and personality traits using NEO personality assessment as a questionnaire has not yet been reported in other research groups. Meanwhile, Stein et al.[42] reported an association between polymorphisms in the genes of norepinephrine pathways and personality traits measured by NEO personality assessment. According to their report, the Ser-49Gly functional polymorphism in the β_1-adrenergic receptor gene (*ADRB1*) that may influences the resting heart rate is associated with extraversion.[42] In addition, Miller et al.[43] studied the relationship between major dimensions of personality and neurophysiological consequence in healthy adults, and reported that blood pressure and urinary levels of norepinephrine were associated with extraversion. Hypothetically, if noradrenergic activity is modulated by functional gene polymorphisms of norepinephrine pathways such as the -3081A/T and Ser-49Gly polymorphisms, extraversion might be linked to sympathetic nervous system activity.

In this study, we did not find a significant association between the 1287G/A and -182T/C NET gene polymorphisms and personality traits measured by NEO-FFI. The 1287G/A polymorphism is a silent mutation that does not affect any amino acid sequences, and it has no known important function.[16] Meanwhile, Jonsson et al.[44] reported that the 1287G/A polymorphism was related to the main norepinephrine metabolite, i.e., 3-methoxy-4-hydroxyphenylglycol (MHPG), concentration in the cerebrospinal fluid (CSF) of healthy volunteers, and the CSF MHPG concentrations with the G/G genotype (without A allele) were higher than those with the G/A and A/A genotypes (with the A allele). In addition, it was reported that urinary levels of MHPG are significantly correlated with reward dependence in Cloninger's temperament dimensions in normal subjects.[45] The -182T/C polymorphism is located in a promoter region.[17] Although the important function of the -182T/C polymorphism is not clear, it is thought that this polymorphism located in the promoter region of the NET gene regulates transcription activity and gene expression. In fact, a previous study indicated that the 5' flanking promoter region of the NET gene comprises approximately 4.7 kb and an additional intron of 476 bp, and several important transcriptional elements containing enhancer sites reside in this intron in the region.[18] Furthermore, Ham et al.[19] suggested that this poly-

morphism is associated with reward dependence in the Korean population. From these observations, we hypothesized that these NET gene polymorphisms may also be related to reward dependence-related traits assessed by NEO-FFI, although there was no association between them in our study.

According to Cloninger's hypothesis,[25,27] a previous study suggested that the NET gene polymorphism might be associated with reward dependence,[19] but most studies did not replicate this finding.[20-24] The different findings in these previous reports may be due to methodological difference such as sample size and statistical procedure. Incidentally, the genotype frequency of 1287G/A polymorphism differs among races. For instance, in Polish people the G/G genotype accounts for 8%, the G/A genotype 47%, and the A/A genotype 45%.[21] The genotype frequency in Polish people is thus different from that in the Japanese determined in this study (χ^2 (2)=117.5, p<0.01). While, in Han Chinese people the G/G genotype accounts for 56%, the G/A genotype 34%, and the A/A genotype 10%.[23] The genotype frequency in Han Chinese people is thus not different from that in the Japanese (χ^2 (2)=2.343, p=0.310). Although both studies showed no relation between the 1287G/A gene polymorphism and personality traits,[21,23] such a difference in genotype frequency among races illustrates a difficulty of the biological approach to elucidating personality formation factors. However, another way to clarify further the effect of the noradrenergic system on the personality dimension of reward dependence, is by utilizing various self-report personality questionnaires with different characteristics.[23] In this study, we found that the NET gene polymorphism is significantly associated with extraversion of reward dependence-related factors, as assessed by NEO-FFI. Therefore, the NET might also be involved in reward dependence of individuals.

In conclusion, our study suggests that the -3081A/T functional promoter polymorphism in the NET gene may affect extraversion, as assessed by NEO-FFI, in Japanese university students. If additional exploration of the NEO five personality dimensions reveals a significant relationship between extraversion and -3081A/T polymorphism, this polymorphism might be useful as a biological marker in analyzing the genetics of psychiatric disorders, and may facilitate diagnosis in psychiatric assessment. However, although all samples in our study were from ostensibly healthy university students, this was not confirmed on the basis of clinical diagnosis by a psychiatrist. Therefore, in our findings, we did not control the possible confounding factor of the presence or absence of a mental disorder in individual participants. Additionally, to study the relationship between the NET gene polymorphism and personality traits, we used only the shortened version of NEO-PI-R in this study. Therefore, we will use the full NEO-PI-R in further studies, which will undoubtedly add further valuable insights into the implications of the association between NET gene polymorphism and personality traits.

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